Protocol Number: P-105-201

Official Title: Phase 2 Multicenter, Randomized, Double-blind, Placebo- Controlled, Multiple Dosing Interval, 2-Period Study of the Safety, Tolerability and Effectiveness of Adoptively Transferred Posoleucel (ALVR105) Multivirus-Specific T Cells in Kidney Transplant Recipients with either High or Low Levels of BK Viremia

NCT Number: NCT04605484

Document Date: 30-Sep-2021

CLINICAL STUDY PROTOCOL

Phase 2 multicenter, randomized, double-blind, placebo-controlled, multiple dosing interval, 2-period study of the safety, tolerability and effectiveness of adoptively transferred posoleucel (ALVR105) multivirus-specific T cells in kidney transplant recipients with either high or low levels of BK viremia

Investigational Product: Posoleucel (ALVR105, formerly known as Viralym-M)
Protocol Number: P-105-201

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FINAL PROTOCOL
Version Number: 4.0
Original Protocol: 06 Jul 2020
Amendment 1: 24 May 2021
Amendment 2: 14 June 2021
Amendment 3: 30 September 2021

DOCUMENT HISTORY

Document	Date
Original Protocol	06-July-2020
Amendment 1 Amendment 2 Amendment 3	24-May-2021 14-June-2021 30-September-2021

AMENDMENT 3: RATIONALE FOR CHANGES

This amendment updates and supersedes Amendment 2 dated 14-June-2021.

Modifications made to the protocol as a part of Amendment 3 and a brief rationale for the changes are summarized below.

Major Revisions include:

- **Eliminated Cohorts A and B**
  - Study now consists of a single cohort with 60 patients with screening (central laboratory) BK viral load between 350 and 10,000,000 copies/mL. Increasing from the previous maximum of 50,000 copies/mL to a maximum of 10,000,000 copies/mL allows for inclusion of a greater number of patients, including those with higher viral loads, in order to include patients with an even greater unmet medical need.

- **Added stratification based on screening BK viral load**
  - Stratum 1 will consist of patients with a BK viral load [redacted] at screening
  - Stratum 2 will consist of patients with a BK viral load [redacted] at screening
  - Stratification will allow for equal randomization among active and placebo arms for patient populations [redacted].

- **Changed local BK viral load (ie, pre-screening values) requirement from 1,000 to <10,000 copies/mL for Cohort A and 10,000 to 50,000 copies/mL for Cohort B to any positive local BK viral load, and clarified that whole blood or plasma results may be used for local BK viral load**
  - Allowing results from local laboratories simplifies screening for sites, while making the final determination of eligibility reliant on the standardized VL testing at the central laboratory to ensure consistent screening data.

- **Allowed local BK viral load (ie, pre-screening values) to be within 90 days prior to screening (instead of 21 days)**
  - Increasing the window for pre-screening simplifies screening for sites, while retaining the rigor and consistency of central laboratory testing for final determination of eligibility.

- **For patients in Period 1 who have undetectable BK plasma viral loads at 2 or more consecutive assessments at least 2 weeks apart and who no longer require dosing visits, allowed subsequent study visits (excluding Weeks 8 and 12) to be conducted by a Sponsor-approved home health vendor in conjunction with a Sponsor-approved telehealth provider**
  - Allowing more home-health visits reduces patient burden.

- **For all patients, allowed study visits after Week 12 to be conducted by a Sponsor-approved home health vendor in conjunction with a Sponsor-approved telehealth provider**
  - Allowing more home-health visits reduces patient burden.

- **Eliminated long-term follow-up period (ie, Weeks 48 to 96)**
  - Study duration is now 26 weeks (2-week screening period, 12-week treatment period, 12-week follow-up period).
  - Patients will be eligible for enrollment in a long-term observational study (ALVR105-401) and will be encouraged to enroll in this study.
  - Eliminating the long-term follow-up reduces patient burden in this study, while allowing more flexible visit timing in the observational study. Also allows twice as much long-term- follow up in the observational study (— up to 4 years— compared to the original protocol).

- **Eliminated sirolimus and everolimus as prohibited medications**
  - Removed from prior/concomitant therapy in exclusion criterion #10 (Section 5.2).
  - Added as medications that cannot be started during the first 12 weeks of the study to Excluded Medications and/or Procedures (Section 6.8.1).
  - Allowing patients with persistent BK viremia whose immunosuppression therapy prior to enrollment included these medications, to allow them to participate in the study, while avoiding the confounding factor of initiating these medications during the treatment period.

- **Added interim administrative analyses and removed interim analyses 1 to 3 from the original protocol**
  - The first administrative interim analysis will be performed by the Sponsor when 12 patients in Stratum 1 [redacted] have completed 8 weeks in the study
  - The second administrative interim analysis will be performed when 30 patients have completed 8 weeks in the study
  - Administrative interim analyses may be omitted or added at the discretion of the Sponsor to allow for long term planning, and to assess ending the study early.

- **Added United States Adopted Name and International Nonproprietary Name, posoleucel, in lieu of ALVR105**

AMENDMENT 2: RATIONALE FOR CHANGES

This amendment updates and supersedes Amendment 1 dated 24-May-2021.

Modifications made to the protocol as a part of Amendment 2 and a brief rationale for the changes are summarized below.

Major Revisions include:

- **Update to Data Safety and Monitoring Board (Section 10.1.5.1)**
  - Removed requirement of pause to enrollment while the DSMB reviews safety data from the first 3 subjects enrolled in each respective cohort. The rationale for this change is that the recently published data demonstrates the well tolerated safety profile of virus-specific 3rd party T cells (VSTs) when used to treat BK virus following kidney transplant. Moreover, the on-going ALVR105 studies of initial treated HCT patients show no reported cases of graft-versus-host disease (GVHD) and/or cytokine release syndrome (CRS), and the infusions were well tolerated.

AMENDMENT 1: RATIONALE FOR CHANGES

This amendment updates and supersedes P-105-201 Original Protocol, dated 06 July 2020, as follows:

Modifications made to the protocol as a part of Amendment 1 and a brief rationale for the changes are summarized below.

Major Revisions include:

- **Updates to Schedule of Activities (Section 1.3)**
  - Shortened maximum screening period from 21 to 14 days. This was done given the change to allow a single viral load at the central lab to qualify a patient, assuming the patient's viral load at the local lab (done as standard of care) is [redacted] copies/mL for Cohort A.
  - Deleted CMV viral load from screening as the CMV-based exclusion criteria has been removed.
  - Amended language to allow for up to 3 home health visits for clinical and viral load assessments in the follow up period after the initial 12 week dosing period. This is done to minimize visits to hospitals and clinics during the COVID-19 pandemic, except when necessary for dosing in the initial 12 week period.
  - Deleted language around locally obtained donor specific antibodies as these are no longer required to qualify since they are obtained in the study.
  - Visit window days have been changed from 14 days to 7 days for weeks 14 to 24, as visits are every 2 weeks during this period of time.

- **Revisions to Inclusion and Exclusion criteria to broaden enrollment (section 5.1 and 5.2 and in Synopsis)**

- Updated the inclusion criteria to remove the 2-year eligibility window after kidney transplant to allow additional patients with BK viremia outside this 2-year post-transplant window to also be eligible.
- Updated the inclusion criteria to eliminate the exclusion for > 12 weeks of BK viremia to also allow participation of patients with stable persistent BK viremia of greater than 12 weeks duration.
- Eliminated the exclusion for > 12 weeks of BK viremia to allow participation of patients with stable persistent BK viremia of greater than 12 weeks duration.
- Removed the 2-year eligibility window after transplant to allow additional patients with BK viremia outside this 2-year post-transplant window to be eligible.
- Removed exclusion for patients with donor specific antibodies at transplant since the data on these antibodies can be accurately compared between central lab data obtained at randomization and subsequently.
- Added belatacept to the list of prohibited medications.

- **Study treatment preparation (section 6.1.2) now refers to the Cell Therapy Manual**
  - IP preparation and infusion procedure description has been removed from the protocol, and referral to the Cell Therapy Manual has been added, as the IP management is more extensively described in the Cell Therapy Manual.

- **Study treatment withdrawal (section 7.1) versus patient discontinuation (section 7.2) after receipt of a prohibited study treatment or after pregnancy.**
  - Clarified by changes in sections 7.1 and 7.2 that patients who receive a prohibited medication or become pregnant may continue in the study for the purposes of observation but are ineligible to receive study treatment.

- **CHARMS study data in section 2.3.2.2 is now referenced to the IB.**
  - As ALVR105 safety and efficacy data from the CHARMS study is more extensively described in the investigational brochure (IB), the specific data have been removed from section 2.3.2.3 and reference to the IB has been added.

- **Miscellaneous revisions to reflect administrative changes, correct typographical errors, or refer to current study documents such as the IB.**
  - Changed references to the study treatment from Viralym-M to ALVR105 to conform to other Allovir protocols.
  - Removed transmission of infectious agent from the list of SAE examples to avoid confusion over whether such an event would always be an SAE.
  - Corrected typographical error that omitted a line in CTCAE grading to now include Grade 5 SAE.
  - Added names of certain the laboratory chemistry values obtained in the study to be consistent with the laboratory manual.

SIGNATURE PAGE

STUDY TITLE:
PHASE 2 MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTIPLE DOSING INTERVAL, 2-PERIOD STUDY OF THE SAFETY, TOLERABILITY AND EFFECTIVENESS OF ADOPTIVELY TRANSFERRED POSOLEUCEL (ALVR105) MULTIVIRUS-SPECIFIC T CELLS IN KIDNEY TRANSPLANT RECIPIENTS WITH EITHER HIGH OR LOW LEVELS OF BK VIREMIA

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature Date

_____ _____

[redacted]
AlloVir

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by AlloVir to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to AlloVir and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by AlloVir, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations, and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

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LIST OF ABBREVIATIONS

Abbreviation	Definition or Term
AdV	adenovirus
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ALVR105 (posoleucel)	Viralym-M
AST	aspartate aminotransferase
ATG	anti-thymocyte globulin
BKV	BK viremia
CBC	complete blood count
CFR	Code of Federal Regulations
CMV	cytomegalovirus
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
CTL	cytotoxic T lymphocyte
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ET	Early Termination visit
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GVHD	graft versus host disease
HBV	hepatitis B virus

Abbreviation	Definition or Term
HC	hemorrhagic cystitis
HCT	hematopoietic cell transplant
HCV	hepatitis C virus
HHV-6	human herpesvirus 6
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HRT	hormonal replacement therapy
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IRB	Institutional Review Board
IRT	interactive response technology
ITT	Intent-to-Treat
IV	Intravenous, -ly
IVIG	intravenous immunoglobulin
JCV	JC virus
MAGIC	Mount Sinai Acute GVHD International Consortium
LLOQ	lower limit of quantification
MDRD	Modified Dose in Renal Disease
MTD	maximum tolerated dose
NCI	National Cancer Institute
PBMC	peripheral blood mononuclear cell
PBO	placebo
Posoleucel; PSL	ALVR105 (Viralym M)
PML	progressive multifocal leukoencephalopathy
PR	partial response
qPCR	quantitative polymerase chain reaction
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SoA	Schedule of Activities

Abbreviation	Definition or Term
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VL	Viral load
Viralym-M	ALVR105 (posoleucel)
WOCBP	woman of childbearing potential
WONCBP	woman of non-childbearing potential

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: Phase 2 multicenter, randomized, double-blind, placebo-controlled, multiple dosing interval, 2-period study of the safety, tolerability and effectiveness of adoptively transferred posoleucel (ALVR105) multivirus-specific T cells in kidney transplant recipients with either high or low levels of BK viremia

Protocol Number: P-105-201

Rationale:

This is a proof-of-concept study of posoleucel (PSL, ALVR105, formerly Viralym-M), and the principal objective is to assess the safety and tolerability of PSL in kidney transplant recipients. The key secondary objective is to test the hypothesis that the administration of PSL to kidney transplant recipients with BK viremia will demonstrate superiority in suppressing BK viral load compared with placebo.

Objectives and Endpoints:

Objectives	Endpoints
Primary • To compare the safety and tolerability of PSL to placebo in kidney transplant recipients	• Treatment-emergent adverse events (TEAEs) and changes in vital signs, physical exams, clinical laboratory assessments, and electrocardiograms (ECGs).
Key Secondary • To assess the overall efficacy of PSL to suppress BK viral load compared with placebo	• Change in BK viremia in patients receiving PSL compared to patients receiving placebo.
Other Secondary • To compare the relative efficacy of different dosing regimens of PSL to placebo	• Change in BK viremia in patients receiving different dosing regimens of PSL compared to patients receiving placebo

Overall Design:

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group multiple dosing interval, 2-period study of the safety, tolerability and efficacy of adoptively transferred PSL virus-specific T cells in kidney transplant recipients with BK viremia.

An independent Data and Safety Monitoring Board (DSMB) will be convened for this study to routinely monitor patient safety; the DSMB will conduct the Interim Analyses according to the DSMB Charter.

This study is comprised of 2 periods. Period 1 includes a 2-week window for screening assessments followed by a 12-week treatment period for eligible patients. Period 2 consists of a 12-week follow-up. Overall, the total duration of patient participation in the study is approximately 26 weeks (2 weeks for screening, 12 weeks of treatment, and 12 weeks of follow-up). The overall enrollment period is anticipated to be approximately 12 months.

Patients will be stratified [redacted]

Brief Summary:

The principal objective of this proof-of-concept study is to assess the safety and tolerability of PSL in kidney transplant recipients with BK viremia. The key secondary objective is to test the hypothesis that the administration of PSL to kidney transplant recipients will demonstrate superiority in suppressing BK viral load compared with placebo.

Condition/Disease

Male and female patients ≥18 years of age:

- who had a kidney transplant performed ≥28 days prior to enrollment, and
- who are diagnosed with BK viremia.

Study Duration

The total duration of patient participation is approximately 26 weeks, including 2 weeks for screening, a 12-week treatment period, and 12 weeks of follow-up.

Treatment Duration

Eligible patients will receive treatment with either PSL or placebo for 12 weeks.

Health Measurement/Observation

Patients will be monitored following randomization for safety, BK viral load, renal function, and immune function, including modification of immunosuppression reduction.

Visit Frequency

Study visits will occur weekly from Day 1 through Day 15, then every other week through Week 24.

Expanded Access

PSL is not available through an expanded access program for this study population.

Intervention Groups and Duration:

Patients will receive infusions of either PSL or placebo for 12 weeks. [redacted] Cryopreservation media (without cells) will serve as the placebo and will be identical in volume and appearance upon administration. All infusions will be administered intravenously (IV) (via peripheral or central line) over approximately [redacted] as a slow push. Patients will receive the same dose for all infusions.

The study will consist of 3 treatment arms. To maintain the blind, all patients will receive an infusion (either PSL or placebo) [redacted] for the first 3 weeks of the dosing period, followed by [redacted]) dosing for the remaining 9 weeks. The treatment arms and associated infusions are as follow:

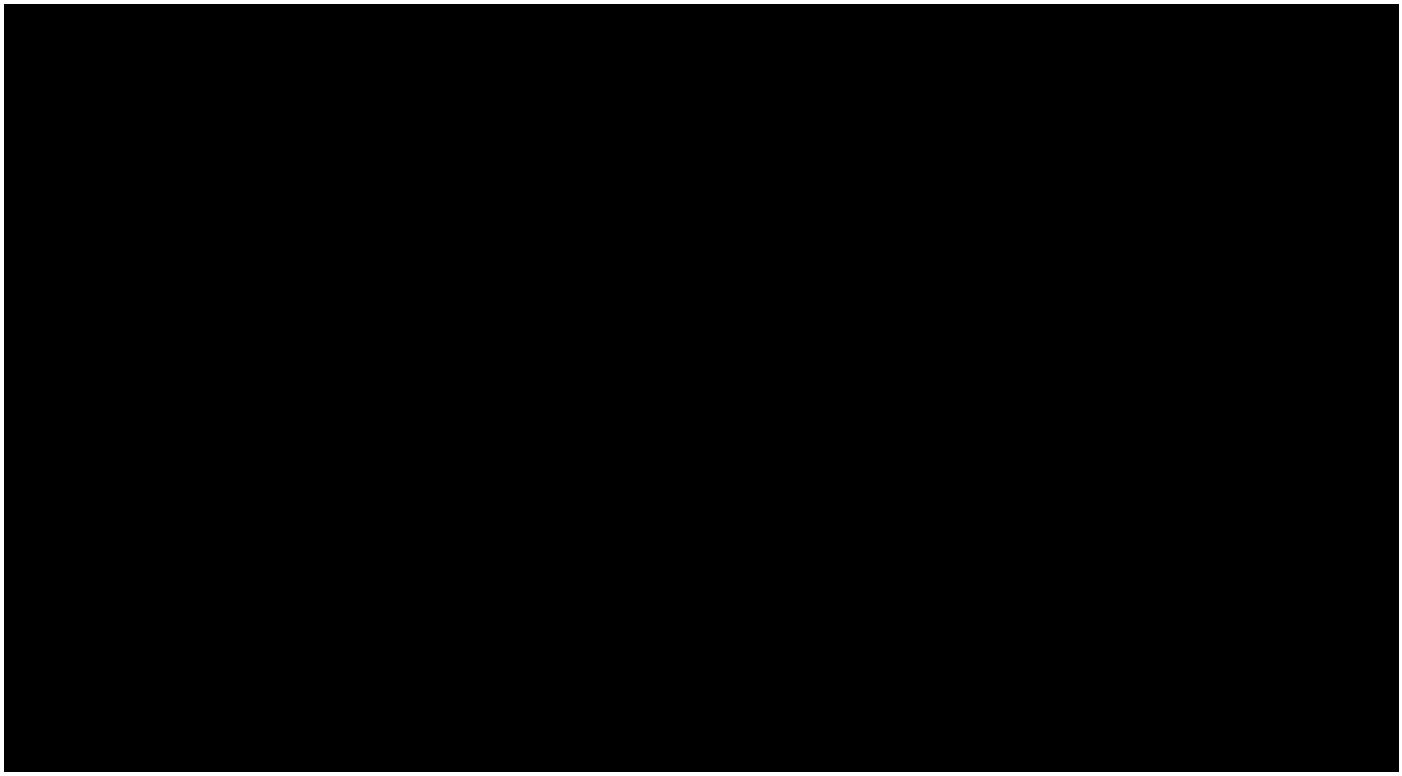
[redacted]

Administrative interim analyses are planned for the study. The Sponsor's study team and Investigators will remain blinded to individual patient data during and after the administrative interim analyses. The first interim analysis will be performed by the Sponsor when 12 patients in Stratum 1 have completed 8 weeks in the study. The second interim analysis will be performed when 30 patients have completed 8 weeks in the study. Interim analyses may be omitted or added at the discretion of the Sponsor to allow for long term planning, and to assess ending the study or either arm early. Stopping rules for the study are detailed in Section 9.5.1.

After the first 3 doses, patients who have undetectable BK plasma viral load at 2 or more consecutive assessments at least 2 weeks apart will discontinue PSL infusions. If a patient's viral load becomes undetectable, the patient may be followed every 14 days for study evaluations as per the Schedule of Activities (SoA) (Section 1.3). No patients are permitted to receive a subsequent infusion of PSL/placebo if they develop new onset graft versus host disease (GVHD) (≥Stage 1; see Appendix 5, Section 10.5) or cytokine release syndrome (CRS >Grade 2; see Appendix 6, Section 10.6) at the proposed time for infusion of any subsequent dose.

1.2 Schema

A summary of study design is shown in Figure 1.



1.3 Schedule of Activities

Table 1 Period 1 (Weeks -2 to 12)

At the discretion of the Investigator, and with the exception of Weeks 8 and 12 (which must be conducted at the site), study visits for patients who have undetectable BK plasma viral load at 2 or more consecutive assessments at least 2 weeks apart after 3 doses may be conducted by a Sponsor-approved home health vendor in conjunction with a Sponsor-approved telehealth provider. These visits may be conducted via video or telephone call.

Study Week	Weeks -2 to -1	Day 1	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Study Day	**-14 to -1**	**1[1]**	**8**	**15**	**29**	**43**	**57**	**71**	**85**
Visit Window (Days)	**NA**	**NA**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Study Procedures									
Informed consent[2]	X								
I/E criteria	X	X							
Demographics	X								
Medical history	X								
Prior & concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events[3]	X	X	X	X	X	X	X	X	X
Complete physical examination[4]	X	X							X
Targeted physical examination[4]			X	X	X	X	X	X	
Weight and height[5]	X	X			X		X		X
Vital signs[6]	X	X	X	X	X	X	X	X	X
12-lead ECG[7]	X	X[7]		X[7]					
Documentation of HLA typing[8]	X								
Clinical labs[9]	X	X		X	X	X	X	X	X
Testing for HIV, HCV, and HBV[22]	X								
BKV plasma viral load[10,11]	X	X		X	X	X	X	X	X
Urine for biomarker[12]		X			X		X		X
AdV, CMV, JCV, HHV-6 plasma, and EBV viral load[10]		X			X		X		X
Pregnancy test	X[13]	X[14]			X[14]		X[14]		X[14]
FSH[15]	X								
Randomization[16]		X							
Provide patient cards		X							

Study Week	Weeks -2 to -1	Day 1	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Study Day	**-14 to -1**	**1[1]**	**8**	**15**	**29**	**43**	**57**	**71**	**85**
Visit Window (Days)	**NA**	**NA**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Study treatment administration[17]		X	X	X	X	X	X	X	X
Post infusion monitoring[18]		X	X	X	X	X	X	X	X
Banked PBMCs for virus specific immunity[19]	X			X	X	X	X		X
Blood for donor DNA[20]					X				X
Kidney biopsy pathologic specimens for review (if clinically indicated)[23]	X	X	X	X	X	X	X	X	X
Donor-specific antibodies [24]		X							X

1. Unless noted otherwise, the Day 1 procedures must be performed within 96 hours of randomization and prior to study treatment administration.
2. Prior to conducting any study-related activities, written informed consent to participate in the study must be provided by the patient.
3. Adverse events will be monitored and documented from randomization through Week 24 in all patients.
4. Complete physical examinations require the patient to be at the site, and will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Targeted physical examinations or assessments will include careful skin examination for GVHD, and other aspects as clinically indicated.
5. Height and weight will be measured at screening; only weight will be measured at other specified later visits. For home visits, stated weight may be used.
6. Includes body temperature, blood pressure, heart rate, and respiration rate and will be measured after resting for 5 minutes. For visits with infusions, vital signs will be measured within 30 minutes prior to infusion, at the end of the infusion, and at 15, 30, 45, and 60 minutes after the end of the infusion. A ±5 minute window will be permitted for all vital sign assessments.
7. Performed within 1 hour after study treatment administration and at the end of study or early termination visit. ECGs will be obtained with the patient in a semi-supine position after a 5-minute rest.
8. The HLA type of the patient and their donor kidney will be obtained from the medical record.
9. CBC must include differential and LFTs must include alkaline phosphatase, bilirubin, AST, and ALT. Urinalysis must be performed.
10. Viral loads of BKV in plasma will be measured. The results of analyses from screening must be available at the time of randomization. Results of central laboratory testing for viral load will be used for the purpose of determining eligibility/inclusion. Additional post-infusion samples may be collected, as clinically indicated. AdV, CMV, JCV, EBV, and HHV-6 viral loads will also be assessed. A whole blood or plasma BK viral load from the local laboratory may be used for the patient to qualify for screening if obtained ≤90 days before the start of screening and with any positive BK viral load (may be reported as either copies/mL or IU/mL).
11. Viral DNA isolated from blood samples will be stored for potential future sequencing/genotyping from the samples collected at baseline for viral load determination. Viral sequencing/genotyping will also potentially be performed in the event of viral recurrence and this sequencing result be compared with the baseline results.
12. Urine samples will be obtained and will be stored for urinary polyomavirus haufen testing.
13. A serum pregnancy test will be performed at screening for all patients of childbearing potential.
14. A urine pregnancy test will be performed at the site prior to study therapy initiation for patients of childbearing potential. If the result is negative, the patient will be eligible for study treatment administration and the remainder of the Day 1 testing/procedures will be performed. If the urine pregnancy result is positive, the patient must not receive study treatment. An on-site urine pregnancy test will also be performed at Weeks 4, 8, and 12 for patients of childbearing potential who are eligible for dosing. Dosing may only be completed following a negative test.
15. FSH will be tested at screening for women of nonchildbearing potential who are postmenopausal, defined as 12 consecutive months with no menses without an alternative medical cause.

16. Randomization will occur after all screening procedures are complete, after all eligibility criteria are met, and prior to study treatment administration. Randomization will mark the end of the screening period. Patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized to receive sequential infusions of PSL cells or placebo.
17. Patients will receive infusions of either PSL or placebo after all blood drawing procedures listed for their visit in the SoA. Patients in the active treatment arms will receive the same [redacted] cells dose for all infusions. Placebo infusions will be administered as appropriate to maintain the blind. As GVHD and CRS are a theoretical safety concern, the incidence and severity of GVHD and CRS will be monitored during the study. No patients are permitted to receive an infusion of PSL or placebo if they develop GVHD (≥Stage 1; see Appendix 5, Section 10.5) or CRS >Grade 2. If any patient develops GVHD or CRS >Grade 2, study treatment infusions should be stopped immediately, and the patient treated per standard of care.
18. Patients will be monitored closely and must remain in the clinic for ≥1 hour after the end of each infusion. Vital signs, including body temperature, heart rate, respiration rate, and blood pressure, will be measured within 30 minutes prior to infusion, at the end of the infusion, and at 15, 30, 45, and 60 minutes after the end of the infusion. A ± 5 minute window is permitted for all vital sign measurements. Patients must also remain on continuous pulse oximetry for ≥30 minutes after the end of the infusion. Post-infusion monitoring should be completed for all infusions of study treatment.
19. Blood will be collected into a cell separation tube and processed to generate a PBMC fraction and a plasma fraction. These fractions will be cryopreserved for potential future evaluation of virus-specific T cell immune function/virus-specific T cell persistence and for potential future evaluation of cytokines and/or other humoral markers of inflammation and/or immune function. In addition, a tube of whole blood will be collected for exploratory determination of virus-specific- T cell immune function in whole blood.
20. Blood will be obtained for (virus-specific T cell) donor DNA quantitation at Weeks 4, 12 and 24. Week 24 DNA may not be quantitated, depending on earlier results.
21. Week 24 procedures should be performed on any patient who terminates the study early before Week 24.
22. Serum will be screened for HIV, HBV and HCV antibodies with reflex nucleic acid testing of plasma.
23. Severity of Biopsy (for clinical indication) Proven Acute Rejection will be adjudicated by a blinded review via expert pathologists. No biopsies are required per the protocol.
24. Donor-specific antibody results should be derived from samples sent to the central laboratory.

Abbreviations: AdV = adenovirus; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BKV = BK viremia; CBC = complete blood count; CMV = cytomegalovirus; CRS = cytokine release syndrome DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; ECG = electrocardiogram; ET = Early Termination Visit; FSH = follicle-stimulating hormone; GVHD = graft versus host disease; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HHV-6 = human herpesvirus 6; HLA = human leucocyte antigen; I/E = inclusion and exclusion; JCV = JC virus; LFT = liver function test; NA = not applicable; PBMC = peripheral blood mononuclear cell; PSL=posoleucel; SoA = Schedule of Activities

Table 2 Period 2 (Weeks 14 to 24; Follow-Up Period)

At the discretion of the Investigator, all study visits during Period 2 may be conducted by a Sponsor-approved home health vendor in conjunction with a Sponsor-approved telehealth provider. These visits may be conducted via video or telephone call.

Study Week	Week 14	Week 16	Week 18	Week 20	Week 22	Week 24/ET [1]
Study Day	99	113	127	141	155	169
Visit Window (Days)	±7 Days	±7 Days	±7 Days	±7 Days	±7 Days	±7 Days
Study Procedures						
Prior & concomitant medications	X	X	X	X	X	X
Adverse events[3]	X	X	X	X	X	X
Targeted physical examination[4]	X	X	X	X	X	X
Weight[5]		X		X		X
Vital signs[6]	X	X	X	X	X	X
12-lead ECG[7]						X
Clinical labs[9]		X		X		X
BKV plasma viral load[10,11]	X	X	X	X	X	X
AdV, CMV, JCV, EBV, and HHV-6 plasma viral load[10]		X		X		X
Banked PBMCs for virus-specific immunity[19]		X		X		X
Blood for donor DNA[20]						X
Obtain any clinically indicated kidney biopsy pathologic specimens for review[23]	X	X	X	X	X	X
Donor-specific antibodies[24]						X

See footnotes and abbreviations following Table 1.

2 INTRODUCTION

AlloVir is developing posoleucel (PSL, ALVR105, formerly Viralym-M), a novel multivirus-specific cellular therapy, to treat a number of serious, virus-associated causes of morbidity and mortality after transplant, including those caused by infection or reactivation with BK viremia ([BKV] and the related polyomavirus JC virus [JCV]), cytomegalovirus (CMV), human herpesvirus 6 (HHV-6), Epstein-Barr virus (EBV), and adenovirus (AdV).

PSL (ALVR105) is a biological product consisting of PSL cells (third-party, multivirus-specific T cells with specificity for BKV, JCV, AdV, HHV-6, EBV, and CMV) in cryopreservation media.

2.1 Study Rationale

This is a proof-of-concept study of PSL, and the principal objective is to assess the safety and tolerability of PSL in kidney transplant recipients with BK virus-associated nephropathy. The key secondary objective is to test the hypothesis that the administration of PSL to kidney transplant recipients will demonstrate superiority in suppressing BK viral load compared with placebo.

2.2 Background

In healthy, immunocompetent individuals, T cell immunity defends against viral infections. In transplant recipients, the use of potent immunosuppressive regimens (and subsequent associated immune compromise) leaves patients susceptible to severe viral infections and diseases. Viral infections are major causes of mortality and morbidity, and they have become leading etiologies for -transplant-related mortality.

BKV is a polyomavirus that causes disease primarily in immunocompromised individuals. After primary infection, the virus remains latent in genitourinary cells. In immunosuppressed kidney transplant recipients, the virus can reactivate and cause tubulointerstitial nephritis, and in some cases, ureteral stenosis (Goldberg 2016). Nephropathy secondary to BKV infection occurs in up to 10% of transplant recipients (Jawdeh 2017) and is usually seen within the first year following transplantation. There are no US Food and Drug Administration (FDA)-approved therapies for BKV infection in kidney transplant recipients. The current treatment consists of reduction in immunosuppression with close monitoring of allograft function; however, immunosuppression reduction may expose kidney transplant recipients to the risk of graft rejection.

The cellular immune response to BKV plays a critical role in the control of BK virus replication. Several immune parameters predict an increased risk of high-level BK viremia; these include a low pre-transplant CD4+ T cell count (DeWolfe 2017), indicators of T cell exhaustion such as T cells with lower production of protective cytokines and interferon (IFN)-ɣ (Mueller 2011), and a lower number of BKV-specific polyfunctional CD8+ T cells (Schmidt 2014).

Thus, development of an adoptively-transferred T cell treatment, such as PSL, may meet an unmet medical need for BKV infection in kidney transplant recipients.

2.3 Posoleucel

Posoleucel (PSL, ALVR105) is a biological product consisting of PSL cells [redacted].

For additional information on PSL, refer to the current Investigator's Brochure (IB).

2.3.1 Overview of Nonclinical Studies with Posoleucel

Consistent with guidance from the FDA, AlloVir proceeded to clinical studies following completion of in vitro studies. No nonclinical animal pharmacology, pharmacokinetic, or toxicology studies of PSL have been conducted or are planned. For additional information related to nonclinical studies with PSL, see the Investigator's Brochure.

2.3.2 Overview of Clinical Studies with Virus-Specific T Cells

2.3.2.1 Results of an Initial Phase 1 Study with Viralym-C

Initially, AlloVir completed a Phase 1 study to assess the safety and efficacy of Viralym-C, a third-party, CMV-specific T cell product, in pediatric and adult allogeneic hematopoietic cell transplant (HCT) recipients with refractory CMV infections (Tzannou 2019). Similar to PSL, Viralym-C is generated from peripheral blood mononuclear cells (PBMCs) after expansion in the presence of overlapping viral peptides and cytokines. Unlike PSL, Viralym-C is only directed against a single virus, CMV. Although Viralym-C is a single virus-specific T cell product, the results of this study support the safety and efficacy of AlloVir's allogeneic, virus-specific T cell products when used in a clinical setting. Briefly, a bank of 8 Viralym-C lines was generated from 8 carefully selected, healthy, CMV-seropositive, transplant donor-eligible volunteers and was predicted to provide a suitably matched cell line for at least 95% of potential patients. Ten patients were treated with Viralym-C: each patient received a single intravenous (IV) infusion of 2×10^7 partially human leukocyte antigen (HLA)-matched virus-specific T cells/m^2 with the option to receive a second infusion after 4 weeks and additional infusions at biweekly intervals thereafter. Of the 10 treated patients, 8 patients received a single infusion and 2 patients required 2 infusions for sustained benefit. There were no immediate infusion-related toxicities, and there were no cases of de novo or recurrent graft versus host disease (GVHD). Based on viral load (measured by quantitative polymerase chain reaction [qPCR]) and/or resolution of signs and/or symptoms, Viralym-C appeared to control CMV infections in all patients with 8 complete responses (CRs) and 2 partial responses (PRs) achieved within 4 weeks of infusion. One patient with CMV retinitis had complete resolution of disease following Viralym-C infusion.

2.3.2.2 Results of the ARMS Study with Donor-Derived Multivirus-Specific T Cells (Administration Of Rapidly Generated Multivirus-Specific Cytotoxic T-Lymphocytes For The Prophylaxis And Treatment Of EBV, CMV, Adenovirus, HHV6, And BK Virus Infections Post Allogeneic Stem Cell Transplant)

In order to broaden the range of viral infections targeted by virus-specific T cells, AlloVir developed donor-derived multivirus-specific T cells with specificity for BKV, AdV, HHV-6, EBV, and CMV. This initial open-label Phase 1/2 study was conducted to assess the safety and toxicity of the multivirus-specific T cells in patients at risk of developing AdV, BKV, CMV, EBV, and/or HHV-6 infections after allogeneic HCT. The first stage of the study was a Phase 1

dose-escalation study to evaluate the safety of 3 dose levels and to determine the maximum tolerated dose (MTD) level. Upon the completion of Phase 1, additional patients were accrued at the MTD level to evaluate a clinically relevant endpoint for antiviral activity in Phase 2.

Patients received [redacted] donor-derived multivirus-specific cytotoxic T lymphocytes (CTLs)/m^2 in a single infusion in the dose-escalation phase of the study, and [redacted] multivirus-specific CTLs/m^2 for the fixed-dose Phase 2 efficacy component (actual number of cells infused ranged between [redacted] cells per patient). Patients were followed for toxicity for 30 days, GVHD for 6 weeks, and antiviral responses for 3 months; long-term follow-up continued for 12 months following the final CTL infusion.

A total of 21 patients were enrolled, and all 21 patients completed the study. All doses were well tolerated. There were no adverse events (AEs) experienced by patients enrolled in the study that were considered treatment related. Three patients developed Stage 2 skin GVHD (Grade 1 overall) and 1 patient developed Stage 3 skin GVHD (Grade 2 overall) in the 6-week initial follow-up period; all patients responded to topical steroids.

2.3.2.3 Results of the CHARMS Study with Third Party-Derived Multivirus-Specific T Cells, Posoleucel (Multivirus-specific T Cells for the Treatment of Virus Infections After Stem Cell Transplant)

To investigate the safety and clinical efficacy of PSL, a multivirus-specific T cell product reactive for BKV, AdV, HHV-6, EBV, and CMV generated from third-party, healthy donors, a Phase 1/2a clinical study was conducted in recipients of allogeneic HCT with drug refractory infections with ≥1 of the 5 viruses targeted by PSL. In this study, patients received a single IV infusion of 2×10^7 partially HLA-matched PSL cells/m^2, with the option to receive a second infusion after 4 weeks (actual range 14 days to >6 weeks) and additional infusions at biweekly intervals thereafter. Therapy with standard antiviral medications could be continued at the discretion of the treating physician.

A total of 58 patients with drug-refractory infections following allogeneic HCT were infused with PSL cell lines matched at 1 to 6 HLA antigens; 54 of these patients completed study treatment and the initial 28-day safety follow-up (the first 38 patients to complete the study are reported in Tzannou 2017). For additional information on PSL, refer to the current Investigator's Brochure (IB).

In addition to patients with post-HCT CMV, EBV, AdV, BKV, and HHV-6-associated infections, patients with JCV infections were also enrolled in this Phase 1/2 study. This decision was based on the homologous nature of BKV and JCV and on results of previous studies. Recently, it was demonstrated that partially HLA-matched third-party BKV-specific T cells could produce similar results in 3 immunosuppressed patients with progressive multifocal leukoencephalopathy (PML). Post-infusion, 2 patients experienced an alleviation of the clinical signs and imaging features of PML while the third patient had a reduction in JCV load and stabilization of symptoms (Muftuoglu 2018). Given these promising results in the context of a complete lack of proven antiviral medications effective against JCV and the potentially devastating natural history associated with JCV, activity of PSL in patients with JCV viremia will be monitored in this study.

2.4 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PSL may be found in the IB.

2.4.1 Potential Benefits

A serious unmet medical need exists for patients experiencing viral infections and diseases such as BKV-associated nephropathy. Up to 10% of kidney transplant recipients will have BK plasma viral loads ≥10,000 copies/mL, a level that is predictive of an allograft biopsy indicating BK virus-associated nephropathy (Hirsch 2013; Bohl 2007; Schachtner 2015), which can progress to graft loss (Gardner 1984). Even with the best current treatments (principally immunosuppression reduction), many centers report allograft nephropathy, rejection, and graft failure more commonly than in non-BK viremic patients (Favi 2019; El-Husseini 2019; Sawinski 2015).

There are no FDA- or European Medicines Agency-approved antiviral therapies for BK viremia or BK virus nephropathy in kidney transplant recipients. The CHARMS study and other related clinical studies strongly suggest that PSL is a safe and effective broad-spectrum therapy to treat commonly observed, severe virus-associated disease in immunocompromised patients. The results of these studies provide preliminary evidence of PSL's efficacy in multiple opportunistic viral infections, including BKV, in immunocompromised patients. Since standard of care immunosuppression reduction in response to persistent high-level BK viremia has been associated with the development of donor-specific antibodies and graft rejection (Sawinski 2015), a therapy such as PSL has the potential to be better than that of standard of care immunosuppression reduction.

2.4.2 Potential Risks

PSL primarily targets cells infected with AdV, BKV (and/or JCV), CMV, EBV, and/or HHV-6. The main risks of administration are inflammation at sites of disease or GVHD due to cross reactivity with the recipient's HLA antigens. Adverse events attributable to virus-specific T cell administration may potentially occur in a small percentage of the treated population. These can include both hematologic and non-hematologic effects, as reported in the CHARMS study.

Studies of donor-derived virus-specific T cells suggest that virus-specific T cells do not persist in patients who receive methylprednisolone in doses ≥1 mg/kg/day. Therefore, if patients develop severe inflammatory reactions thought to be attributable to PSL, a therapeutic option is to administer methylprednisolone (1 to 2 mg/kg/day). In patients who develop skin rash or skin GVHD, excellent responses have been seen with administration of topical steroids.

As with other biological therapies delivered by IV infusion, possible side effects of PSL infusion include allergic reaction (anaphylaxis), decreased oxygenation, nausea/vomiting, arrhythmia, and hypotension.

A detailed breakdown of the time points for blood sample collection during the course of this study is provided in in Section 1.3.

In order to minimize the volume of blood collected during the study, the blood volume of individual samples has been reduced to the maximum extent feasible. This has been done in a manner that is expected to maintain the scientific integrity of the study while minimizing the risks to patients.

No single blood draw will exceed approximately 72 mL, and the total blood volume collected during the first 8 weeks of the study will be approximately 280 mL (~4 mL/kg for a 70 kg patient). Over the entire 26-week course of the study, the total blood volume collected is outlined in the laboratory manual.

For the collection of other study-related material from patients, there are no invasive procedures that are required for the study conduct beyond those procedures being used for the routine clinical care of these patients.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary • To compare the safety and tolerability of PSL to placebo in kidney transplant recipients	• Treatment-emergent adverse events (TEAEs) and changes in vital signs, physical exams, clinical laboratory assessments, and electrocardiograms (ECGs)
Key Secondary • To assess the overall efficacy of PSL to suppress plasma BK viral load compared with placebo	• Change in BK viremia in patients receiving PSL compared to patients receiving placebo
Other Secondary • To compare the relative efficacy of different dosing regimens of PSL to suppress BK viral load versus placebo	• Change in BK viremia in patients receiving different dosing regimens of PSL compared to patients receiving placebo
Exploratory • To assess change in estimated glomerular filtration rate (eGFR) over 24 weeks in recipients of PSL versus placebo	• Change in eGFR by Modified Dose in Renal Disease (MDRD) formula in recipients of PSL versus placebo
• To identify changes in donor-specific anti-human leukocyte antigen (anti-HLA) antibodies in recipients of PSL versus placebo	• Changes from baseline in levels of donor-specific anti-HLA antibodies in recipients of PSL versus placebo
• To determine the proportion of patients with resolution of BK viremia at 8 weeks post virus-specific T cell infusion	• Proportion of patients with resolution of BK viremia at 8 weeks post - Virus-Specific T cell infusion
• To assess kidney allograft survival at 24 weeks	• Proportion of patients with eGFR >20 mL/min at 24 weeks
• To assess the incidence of recrudescent or new infections with target viruses (including cytomegalovirus [CMV]), but principally BKV	• Incidence of new target viral infections or recrudescent infections (ie, BKV, CMV, EBV, AdV, JCV, and/or HHV-6) as defined by onset of viremia and/or the presence of associated symptoms relative to baseline. • Length of BKV remission (ie, time from clearance of BK viremia to reappearance of BK viremia [plasma viral load >156 copies/mL × 2 measures that are at least 2 weeks apart] or end of study)

• To determine whether patients with initially low BK viral load (ie, <10,000 copies/mL) can be prevented from developing viremia ≥10,000 copies/mL that leads to new or increased immunosuppression reduction • To determine whether patients with initially low BK viral load (ie, <10,000 copies/mL) in the investigational arm(s) develop lower viral loads than the placebo arm	• Number of patients with screening BK viremia <10,000 copies/mL who develop BK viremia ≥10,000 copies/mL (sustained or non-sustained) or who experience a medically significant event that leads to changes in immunosuppression reduction • The absolute viral load in patients in the investigational arms versus that in patients in the placebo arm with screening BK viremia <10,000 copies/mL.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, multiple dosing interval, 2-period study of the safety, tolerability and efficacy of adoptively transferred PSL virus-specific T cells in kidney transplant recipients with BK viremia.

This study is comprised of 2 periods. Period 1 includes a 2-week window for screening assessments followed by a 12-week treatment period for eligible patients. Period 2 consists of a 12-week follow-up. Overall, the total duration of patient participation in the study is approximately 26 weeks (2 weeks for screening, 12 weeks of treatment, and 12 weeks of follow-up). The overall enrollment period is anticipated to be approximately 12 months.

The protocol defines standardized consensus guidelines for the type of immunosuppression reduction in order to systematize the approach to immunosuppression reduction across sites (Appendix 7, Section 10.7). Administration of PSL in the active arms of the study may result in fewer patients meeting the criteria for initiation or intensification of immunosuppression reduction according to the protocol at their institution than in the placebo arm of the study, and changes to each patient's immunosuppression will be monitored.

Patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized to receive PSL or placebo infusions. Patients will be stratified [redacted] Patients will be monitored following randomization for safety, BK viral load, renal function, and immune function, including modification of immunosuppression reduction.

Patients will receive infusions of either PSL or placebo for 12 weeks. The specific PSL cell line for infusion will be selected [redacted]. Cryopreservation media (without cells) will serve as the placebo and will be identical in volume and appearance upon administration. All infusions will be administered intravenously (IV) (via peripheral or central line) over approximately [redacted] as a slow push. Patients will receive the same dose for all infusions.

The study will consist of 3 treatment arms. To maintain the blind, all patients will receive an infusion (either PSL or placebo) [redacted] The treatment arms and associated infusions for Cohort A are as follow:

- [redacted]
- [redacted]

- [redacted]

Administrative interim analyses are planned for the study. The Sponsor's study team and Investigators will remain blinded to individual patient data during and after the administrative interim analyses. The first interim analysis will be performed by the Sponsor when 12 patients in Stratum 1 have completed 8 weeks in the study, and the second interim analysis will be performed when 30 patients have completed 8 weeks in the study. Interim analyses may be omitted or added at the discretion of the Sponsor to allow for long term planning, and to assess ending the study or either arm early, as described in the statistical analysis plan (SAP). See Figure 1 for a schematic representation of the study design.

Stopping rules for each dosing interval arm and for the study are detailed in Section 9.5.1.

After the fi[redacted]3 doses, patients who have undetectable BK plasma viral load at 2 or more consecutive assessments at least 2 weeks apart will discontinue PSL infusions. If a patient's viral load becomes undetectable, such a patient may be followed every 14 days for study evaluations as per the Schedule of Activities (Section 1.3). No patients are permitted to receive a subsequent infusion of PSL if they develop new onset GVHD (≥Stage 1; see Appendix 5, Section 10.5) or cytokine release syndrome (CRS) (>Grade 2; see Appendix 6, Section 10.6) at the proposed time for infusion of any subsequent dose.

An independent Data and Safety Monitoring Board (DSMB) will be convened for this study to routinely monitor patient safety and evaluate prespecified interim analyses to stop the study early (see Section 10.1.5).

4.2 Scientific Rationale for Study Design

Even with the best current treatments (principally immunosuppression reduction), many centers report allograft nephropathy, rejection, and graft failure more commonly in patients with BK viremia than in those without (Favi 2019, El-Husseini 2019, Sawinski 2015). The unmet medical need in BK virus nephropathy is reflected in the continued use of (ineffective) antiviral treatments such as leflunomide, cidofovir, intravenous immunoglobulin G, and levofloxacin concurrently with immunosuppression reduction (Bruminhent 2019).

PSL multivirus-specific T cells target BK virus infected cells, and thus offer a way to lower viral load in BK viremic kidney transplant recipients at risk for BK nephropathy. To date, immunosuppression reduction is the only therapy that has succeeded in lowering BK viral load, and even it has had limited success and can lead to increased risk of rejection and/or production of donor-specific antibodies. This proof-of-concept study will also identify the dosing interval for virus-specific T cell infusions needed to lower viral load in kidney transplant recipients on continued immunosuppression and potentially limit the damage caused by BK virus replication in the kidney allograft.

The use of placebo in this clinical study is justified for the following reasons:

1) A placebo control group is required to provide an objective, contemporaneous assessment of the therapeutic effects and AE profile of PSL.
2) The use of an active control group in the study is not feasible since there are no approved, efficacious antiviral therapies for the treatment of BKV infections.

3) Investigators are permitted to administer standard of care immunosuppression reduction as per the algorithm included in Appendix 7 (Section 10.7).

4.3 Justification for Dose

PSL is to be administered at a fixed cell dose. The fixed dose was selected based on data from previous clinical studies in which PSL cells were well tolerated, safe, and effective.

[redacted]

The use of PSL in a solid organ transplant population that may be receiving several different chronic immunosuppressive agents justifies the need for dose interval ranging in this study. [redacted]; to date, there are no data for the use of PSL in the setting of solid organ transplant. The use of other T cell regimens for the treatment of viral infections specific to the solid organ transplant setting has demonstrated preliminary efficacy and safety when cell are administered weekly for 3 weeks followed by a variable period of rest, depending on the presence or absence of disease progression (Prockop 2019). Two-week -Virus-Specific T cell dosing intervals have been described in several studies in which suppression of BK viral load was observed; however, an incomplete and/or delayed virologic response was often observed (Flower 2020). [redacted] During this time, clinical safety and viral load will be monitored very closely by the DSMB. T cell persistence data will also be collected.

4.4 End of Study Definition

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last patient in the study.

A patient is considered to have completed the study if he/she has completed all phases of the study including the Week 24 visit.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Age

1. Patients must be ≥18 years of age at the time of signing the informed consent.

Type of Patient and Disease Characteristics

2. Patients who had a kidney transplant performed ≥28 days prior to enrollment.
3. BKV, based on the following criteria (both criteria a and b must be met):
    a. Any positive whole blood or plasma BK viral load at a local laboratory obtained ≤90 days before the start of screening.
    b. Confirmation of BK viremia of 350 copies/mL – 10,000,000 copies/mL as determined by the central laboratory at screening.
4. At least 1 identified, suitably matched PSL cell line for infusion is available.

Sex

5. Male and/or female

    Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

    a. Male patients:

    Male patients are eligible to participate if they agree to the following during the study treatment period and for at least 90 days after the last dose of study treatment:

    - Refrain from donating sperm

    PLUS, either**:**

    - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

    OR

    - Must agree to use contraception /barrier as detailed below
        - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant b. Female patients:
    - A female patient is eligible to participate if she is not pregnant or breastfeeding, and 1 of the following conditions applies:

- She is a woman of non-childbearing potential (WONCBP) as defined in Section 10.4.1

OR

- She is a WOCBP and using an acceptable contraceptive method as described in Section 10.4.2 during the study treatment period and for at least 90 days after the last dose of study treatment. The Investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study treatment.

- A WOCBP must have a negative highly sensitive serum pregnancy test within 21 days before the first dose of study treatment, see Section 8.2.5.
- Additional requirements for pregnancy testing during and after study treatment are located in Section 8.2.5.
- The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

6. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 Exclusion Criteria

Medical Conditions

1. Undergone allogeneic hematopoietic cell transplantation.
2. Evidence or history of GVHD or CRS (Appendix 5 [Section 10.5] and Appendix 6 [Section 10.6], respectively).
3. Uncontrolled or progressive bacterial or fungal infections (ie, evidence of bacteremia, fungemia, dissemination, and/or organ-specific infection not well controlled by present therapies).
4. Uncontrolled or progressive viral infections (ie, evidence of viremia, dissemination, and/or organ-specific infection not well controlled by present therapies) not targeted by PSL.
5. Uncontrolled or progressive EBV-associated post-transplant lymphoproliferative disorder.
6. Known or presumed pneumonia.
7. Hemodynamic or respiratory instability defined as either of the following:
    a. Requirement for continuous infusions of inotropes or vasopressors for blood pressure support.
    b. Requirement for endotracheal intubation or mechanical ventilation.

8. Evidence of any medical condition that in the opinion of the Investigator might interfere with the patient's ability to participate in the trial.

Prior/Concomitant Therapy

9. Ongoing therapy with high-dose systemic corticosteroids (ie, prednisone dose >0.5 mg/kg/day or equivalent).
10. Patients who received, or are planned to receive, abatacept or belatacept, within 3 months of screening, or who received equine anti-thymocyte globulin ([ATG] Atgam®) or rabbit ATG (Thymoglobulin ®) in doses of >4.5 mg/kg or alemtuzumab (Campath-1H) or other immunosuppressive T cell-targeted monoclonal antibodies <28 days prior to randomization.

Prior/Concurrent Clinical Study Experience

11. Receipt of other investigational antiviral treatments (eg, anti-BK monoclonal antibodies) within 28 days or 5 half-lives (whichever is longer) prior to randomization.

Diagnostic assessments

12. Liver dysfunction, defined as liver transaminases (ie, aspartate aminotransferase or alanine aminotransferase) >5 times the upper limit of normal (ULN) or direct bilirubin >2 times the ULN reference per local laboratory.
13. Renal dysfunction, defined as estimated glomerular filtration rate (eGFR) (estimated by Modified Dose in Renal Disease [MDRD] formula) <20 mL/min/1.73 m^2.

Other Exclusions

14. Pregnant or nursing or planning to become pregnant.
15. ABO incompatible or complement-dependent lymphocytotoxic crossmatch positive transplant (isolated positive B cell crossmatches are not an exclusion criterion).
16. Weight <40 kg.
17. History of hypersensitivity to any of the components of the Investigational Product.

5.3 Lifestyle Restrictions

This section is not applicable.

5.3.1 Meals and Dietary Restrictions

This section is not applicable.

5.3.2 Caffeine, Alcohol, and Tobacco

This section is not applicable.

5.3.3 Activity

This section is not applicable.

5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not randomized into the clinical study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs). If a matching PSL line is not available, resulting in the patient being a screen failure, the HLA type data will be collected in addition to the minimal information required to meet the Consolidate Standards of Reporting Trials.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened following discussion with, and approval of, the Sponsor.

6 STUDY TREATMENT(S) AND CONCOMITANT THERAPY

Study treatment is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study patient according to the study protocol.

6.1 Study Treatment(s) Administered

PSL is a third-party, donor-derived, "off-the-shelf," Virus-specific T cell product with specificity for BKV, AdV, CMV, EBV, and HHV-6 (with additional cross-reactive specificity for JCV) that is cryopreserved and ready for immediate use. The placebo arm will receive separate IV infusions of cryopreservation media (without cells) as placebo.

For more information, see the Investigator's Brochure.

PSL cell lines will be checked for cell concentration, viability, identity, phenotype, potency, endotoxin, mycoplasma, and sterility.

Table 3 Study Treatment Information

Arm Name	[redacted]	[redacted]	**Placebo**
Intervention Name	PSL	PSL	Placebo
Type	Drug	Drug	Drug
Dosage formulation	Ampule (Cryovial)	Ampule (Cryovial)	Ampule (Cryovial)
Unit dose strength(s)	[redacted]	[redacted]	[redacted]
Dosage Level(s)	[redacted] PSL cells [redacted]	[redacted] PSL cells [redacted]	Placebo [redacted]
Route of Administration	IV slow push [redacted]	IV slow push [redacted]	IV slow push [redacted]
Use	Experimental	Experimental	Placebo control
IMP and NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Study treatment will be provided in cryovials. Each cryovial will be labeled as required per country requirement	Study treatment will be provided in cryovials. Each cryovial will be labeled as required per country requirement	Study treatment will be provided in cryovials. Each cryovial will be labeled as required per country requirement
Current/ Former Name(s) or Alias(es)	Posoleucel/ALVR105, Viralym M	Posoleucel/ALVR105, Viralym M	Not applicable

Abbreviations: IMP = investigative medicinal product; IV = intravenous; Q = every.

6.1.1 Cell Line Selection

PSL cell lines will be selected for each patient based on an overall HLA match [redacted] as outlined below. The HLA alleles used for evaluation of matching are HLA-A, HLA-B, HLA-DR, and HLA-DQ.

The appropriate study treatment (ie, the cell lines for infusion) for patient administration will be selected [redacted]

6.1.2 Study Treatment Administration

Randomization of patients to PSL versus placebo will occur only after cell line matching and selection has been confirmed (to satisfy inclusion criteria).

Premedication is not required, except for patients with a prior history of reaction to blood products. These patients may receive premedication with 0.25 to 0.5 mg/kg (maximum dose of 25 mg) diphenhydramine (IV or oral) and/or 5 to 10 mg/kg (maximum dose of 1000 mg) acetaminophen (IV or oral) prior to study treatment administration. Premedication with corticosteroids is prohibited.

At or close to the time of administration, the product will be thawed. For further details on product preparation prior to infusion, please see the Cell Therapy Manual.

Patients will be monitored according to institutional standards for the administration of blood products and, at a minimum, according to the following requirements:

- Patients in an outpatient setting must remain in the clinic for ≥1 hour after the end of the infusion.
- Patients must remain on continuous pulse oximetry for ≥30 minutes after the end of the infusion.
- Vital signs will be monitored within 30 minutes prior to the infusion, at the end of infusion, and at 15, 30, 45, and 60 (±5) minutes after the end of the infusion.

All findings must be recorded in the electronic case report form (eCRF).

Patients will receive supportive care for acute or chronic toxicity, including blood components, antibiotics, or other interventions as appropriate per local treatment guidelines. See Section 6.8.2 for additional information.

If a patient experiences an infusion reaction, 0.25 to 0.5 mg/kg (maximum dose of 25 mg) diphenhydramine (IV or oral) and/or 5 to 10 mg/kg (maximum dose of 1000 mg) acetaminophen

(IV or oral) may be administered as treatment. The maximum recommended single and daily doses of diphenhydramine and acetaminophen should not be exceeded. In the case of suboptimal control of an infusion reaction or the need to use corticosteroids for treatment of an infusion reaction, doses of ≤0.5mg/kg/day of prednisone or equivalent should be considered first.

6.2 Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Cell Therapy Manual.

6.2.1 Study Treatment Preparation and Dispensing

PSL and placebo will be supplied in cryovials, which are to be transported from vapor phase liquid nitrogen storage at the clinical site to the cell-thawing and preparation location in a liquid nitrogen dewar or other suitable container. Details of the cell thawing, preparation for dosing, and administration to the patient will be provided to clinical sites in a separate Cell Therapy Manual.

6.2.2 Storage and Accountability

PSL or placebo is stored in the vapor phase of liquid nitrogen in a continuously monitored storage freezer.

All material containing PSL or placebo will be treated and disposed of as hazardous waste in accordance with governing regulations and clinical site procedures.

PSL and placebo accountability are the responsibility of the Principal Investigator and Sponsor. However, this responsibility may be delegated to a suitably qualified Investigator or designee who has had appropriate study-specific training that has been documented. The Sponsor will maintain records that will allow anonymous traceability of each PSL cell line to the third-party PBMC donor from whom it originated. These records will be maintained for 30 years after expiry for each cell line.

Detailed records will be maintained to allow for accurate accountability of PSL and placebo as per applicable Sponsor and clinical site procedures. For further details and specifications, see the Cell Therapy Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

This study is blinded to safeguard the integrity of the AE determination process, and to ensure that decisions regarding discontinuation of infusions for apparent efficacy are made in an unbiased fashion.

Study using IVRS/IWRS	All patients will be centrally assigned to randomized study treatment using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS will be provided to each site. Study treatment will be dispensed at the study visits summarized in the Schedule of Activities (SOA, Section 1.3).

The Sponsor designee (eg, interactive response technology [IRT] vendor) will have a designated randomization administrator who will maintain the randomization codes in accordance with standard operating procedures to ensure the blind integrity is properly maintained. Care should be exercised to ensure that only Sponsor personnel who require knowledge of treatment assignments will be unblinded (eg, staff involved in Suspected Unexpected Serious Adverse Reaction [SUSAR] reporting).

Blind Break (IVRS/IWRS)	The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patients' intervention assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a patient's intervention assignment unless this could delay emergency treatment of the patient. If a patient's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

Unblinding should only occur in the event of an emergency or AE for which it is necessary to know the study treatment to determine an appropriate course of therapy. If the patient's study treatment must be unblinded, the Investigator or qualified designee should contact IRT for the study treatment information. The IRT documentation indicating the blind break at the site must be retained with the patient's source documentation in such a way as to avoid unblinding the treatment assignment to other site or Sponsor blinded personnel.

If possible, the Investigator should attempt to contact the Medical Monitor prior to unblinding. If not possible, the Investigator should notify the Medical Monitor as soon as possible of the unblinding without disclosing the treatment assignment of the unblinded patient. The Investigator must document the patient's identification, the reason for breaking the blind, and the date and time for breaking the blind. Following unblinding, the Investigator must withdraw the patient from the study.

6.4 Study Treatment Compliance

When patients are dosed at the site, they will receive study treatment directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and on the appropriate eCRF. The dose of study treatment and study patient identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

6.5 Dose Modification

This section is not applicable.

6.5.1 Retreatment Criteria

As GVHD is a theoretical safety concern, the incidence and severity of GVHD will be monitored during the study. No patients will be permitted to receive a subsequent infusion of PSL if they develop new onset GVHD (≥Stage 1; see Appendix 5, Section 10.5) or CRS (>Grade 2; see Appendix 6, Section 10.6).

After the first 3 doses, patients who have undetectable BK plasma viral load at 2 or more consecutive assessments at least 2 weeks apart will discontinue PSL infusions. If a patient's viral load becomes undetectable in this way such patients may be followed every 14 days for study evaluations as per the SoA (Section 1.3).

6.6 Continued Access to Study Treatment after the End of the Study

No further treatment will be provided after the last dose of PSL (or placebo) after Week 12. However, patients will continue in the study for evaluation of safety, efficacy, and other endpoints for an additional 12 weeks.

6.7 Treatment of Overdose

For this study, any dose of PSL greater than [redacted] cells within a 24-hour period (±1 hour) will be considered an overdose.

As there is no antidote, the Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

- Contact the Medical Monitor immediately.
- Evaluate the patient to determine, in consultation with the Medical Monitor, whether study treatment should be interrupted or whether the dose interval should be extended.
- Closely monitor the patient for any AE/SAE and laboratory abnormalities until the next dosing day.
- Document the quantity of the excess dose as well as the duration of the overdose.

6.8 Concomitant Therapy

All medications, including transplant immunosuppression, used within 30 days before screening will be recorded. All concomitant medications and concurrent therapies will be documented as

indicated in Section 1.3. Dose, route, unit frequency of administration, indication for administration, and dates of medication will also be captured in source documents and on the appropriate eCRF.

Clinically available (ie, not investigational) antiviral agents prescribed for other infections, such as foscarnet and ganciclovir to treat CMV, are allowed. Data on their use will be collected along with other concomitant medications.

Standard of care immunosuppression reduction is permitted as per the guidelines for the type of immunosuppression reduction that are provided in Appendix 7 (Section 10.7). The typical immunosuppression regimen for kidney transplant patients, which includes a calcineurin inhibitor, an anti-metabolite, commonly mycophenolate mofetil or mycophenolic acid, with or without low dose prednisone, is included in Section 10.7, Figure 2. If a patient's immunosuppression regimen includes sirolimus or everolimus, a change in these agents based on BK viral load is not usually made; for this reason they are not included in Figure 2, and patients taking these medications who require changes in dose of their sirolimus or everolimus will require discussion with the Medical Monitor. These guidelines should be followed in order to standardize the approach to immunosuppression across sites. Administration of PSL in the active arms of the study may result in fewer patients meeting the criteria for modification of immunosuppression reduction according to the protocol at their institution than in the placebo arm of the study, and changes to each patient's immunosuppression will be monitored and may be summarized as an exploratory endpoint.

6.8.1 Excluded Medications and/or Procedures

All patients may receive available supportive therapy with approved treatments, but initiation of therapy *for the attempted treatment of BK virus infection* with sirolimus, everolimus, cidofovir, brincidofovir, fluoroquinolones (eg, ciprofloxacin), intravenous immunoglobulin (IVIG) or leflunomide during the first 12 weeks after randomization is prohibited.

Receipt of other investigational antiviral treatments (eg, anti-BK virus monoclonal antibodies) within 28 days or 5 half-lives (whichever is longer) prior to randomization and throughout the duration of the study is prohibited.

T cell ablative therapies such as antithymocyte globulin, alemtuzumab (Campath-1H), or other immunosuppressive T cell-targeted monoclonal antibodies are prohibited during the study. Daily doses of corticosteroids exceeding 0.5 mg/kg prednisone (or equivalent) are also prohibited during the study.

6.8.2 Supportive Care

The following supportive care measures are permitted:

- Analgesics
- Narcotics
- IV hydration
- Bladder irrigation
- Antispasmodics

- Transfusion of red blood cells (RBCs)
- Transfusion of platelets
- Transfusion of fresh frozen plasma
- Nephrostomy tube placement

All supportive care measures must be documented in the patient study records and the eCRF.

6.8.3 Rescue Medication

This section is not applicable.

7 DISCONTINUATION OF STUDY TREATMENT AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

The following criteria do not necessitate withdrawal from the study, but do render the patient ineligible to receive any additional infusions of study treatment:

1. Development of ≥ Grade 1 acute GVHD within 6 weeks, or a Grade 3 to 4 non-hematologic AE within 4 weeks from last PSL dose that is considered related to study treatment administration. If this occurs, the patient's toxicities will be followed until resolution or until the patient's participation in the study ends.
2. Receipt of any other hematopoietic stem cell product.
3. Receipt of therapy for new malignancy.
4. Occurrence of Grade 3 or 4 CRS. If this occurs, the patient's toxicities will be followed until resolution or until the patient's participation in the study ends.
5. Requirement for prohibited concomitant medication
6. Pregnancy

If any of the above criteria are met, every effort should be made to keep the patient in the study and continue follow-up.

7.1.1 Rechallenge

This section is not applicable.

7.2 Patient Discontinuation/Withdrawal from the Study

Participation of a patient in this clinical study may be discontinued for any of the following reasons:

- The patient withdraws consent
- The patient requests discontinuation from the study for any reason
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol
- Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the patient
- Patient failure to comply with protocol requirements or study-related procedures
- Termination of the study by the Sponsor or the regulatory authority

If a patient withdraws prematurely from the study due to the above criteria or for any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the Week 24 (Day 169) Visit. The reason for patient withdrawal must be documented in the eCRF.

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

Withdrawn patients will not be replaced.

7.3 Lost to Follow up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 in Section 10.1.9.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (eg, blood count, local BK viral load, etc.) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- At the discretion of the Investigator, and with the exception of Weeks 8 and 12 (which must be conducted at the site), study visits for patients who have undetectable BK plasma viral load at 2 or more consecutive assessments at least 2 weeks apart after 3 doses may be conducted by a Sponsor-approved home health vendor in conjunction with a Sponsor-approved telehealth provider. These visits may be conducted via video or telephone call.
- For all patients, at the discretion of the Investigator, study visits after Week 12 may be conducted by a Sponsor-approved home health vendor in conjunction with a Sponsor-approved telehealth provider. These visits may be conducted via video or telephone call.
- Results (eg, Safety/Laboratory/analyte) that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- The maximum amount of blood collected from each patient over the duration of the study is outlined in the laboratory manual.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA.

8.1.1 Viral Load

In patients with concomitant viral infections at the time of treatment, peripheral blood and, where relevant, urine, will be monitored for BKV, CMV, AdV, EBV, JCV, and/or HHV-6 viral load (see Section 1.3). Resolution of viral infection will be defined as a return to undetectable as defined by the assay used and complete resolution of clinical signs and symptoms as determined by the Investigator. Viral load will be quantitated using polymerase chain reaction assays.

Samples for viral sequence/genotype will be collected on all patients as indicated in Section 1.3.

8.1.2 Estimated Glomerular Filtration Rate

Estimated glomerular filtration rate will be calculated from serum creatinine using the MDRD equation.

8.1.3 Human Leukocyte Antigen Antibodies

Human leukocyte antigen antibodies will be assessed using a flow cytometric method.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA in Section 1.3.

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. A targeted physical examination will include careful skin examination for GVHD, and other systems as clinically indicated.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Physical examinations will be performed and height and weight will be collected as indicated in Section 1.3. The complete physical examination will be performed by the Investigator or another qualified member of the site's study team. New abnormal physical examination findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

8.2.2 Vital Signs

- Temperature, pulse rate, respiratory rate, pulse oximetry, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse, and respiratory rate.
- For visits with infusions, vital signs will be measured within 30 minutes prior to infusion, at the end of the infusion, and at 15, 30, 45, and 60 (±5) minutes after the end of the infusion.

8.2.3 Electrocardiograms

Single 12-lead electrocardiograms (ECGs) will be obtained with the patient in a semi-supine position after a 5-minute rest, as outlined in the SoA (see Section 1.3). The ECG machine will be one that automatically calculates the heart rate and measures PR, QRS, QT, and QTc (corrected using Fredericia's and Bazett's methods) intervals.

8.2.4 Clinical Safety Laboratory Assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the patient's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
    - All protocol-required laboratory tests, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
    - If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.2.5 Pregnancy Testing

A serum pregnancy test will be performed at screening for all patients of childbearing potential. A urine pregnancy test will be performed monthly for patients who are of childbearing potential. See Section 1.3.

8.2.6 Suicidal Ideation and Behavior Risk Monitoring

This section is not applicable.

8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 3 in Section 10.3.

The definitions of unsolicited and solicited AEs can be found in Appendix 3 (Section 10.3).

Adverse events will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the patient to discontinue study treatment (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected at the time points specified in the SoA (Section 1.3) from randomization until study participation is complete.

Medical occurrences that begin before randomization but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions, not as AEs.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.3.7), will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will

review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.3.4.1 Expedited Reporting

The Sponsor/designee will report all relevant information about SUSARs that are fatal or life-threatening as soon as possible to the FDA, applicable competent authorities in all the Member States concerned, and the Central Ethics Committee, and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the FDA, applicable competent authorities concerned, and the Central Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to the investigational medicinal product.

8.3.5 Pregnancy

- Details of all pregnancies in female patients and female partners of male patients will be collected after the start of study treatment and until 90 days after the last dose of study treatment.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy of the female patient or female partner of a male patient (after obtaining the necessary signed informed consent from the female partner).
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The female patient or pregnant female partner of a male patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the female patient or pregnant female partner of a male patient and the neonate and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in

former study female patients or pregnant female partners of a male patients, he or she may learn of an SAE through spontaneous reporting.

- Should a female patient become pregnant during the course of a study, under certain circumstances the study design may allow for the continuation of study treatment. In these instances, International Council on Harmonisation (ICH) Guidelines and local regulations must be observed, and appropriate justification given in Section 4.2. In the absence of such justification female patients who become pregnant must be discontinued from study treatment.

Prior to continuation of study treatment following pregnancy, the following must occur:

- The Sponsor and the relevant IRB/IEC give written approval.
- The patient gives signed informed consent.
- The Investigator agrees to monitor the outcome of the pregnancy and the status of the patient and her offspring.

8.3.6 Cardiovascular and Death Events

This section is not applicable.

8.3.7 Adverse Events of Special Interest

Adverse events of special interest (AESI) include infusion-related AEs, GVHD, and CRS. Grading criteria for GVHD and CRS can be found in Appendix 5 (Section 10.5) and Appendix 6 (Section 10.6), respectively. These AESIs will be reviewed by the DSMB as per the DSMB Charter.

8.3.7.1 Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgement should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the patient has received additional dose(s) or the Investigator has reason to suspect that the patient has received additional dose(s).
- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, patient, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired

product are always reportable as medication errors; cases of patients missing doses of investigational product are not considered reportable as medication errors.

- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A Special Situations Report Form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events as described above must be reported on the Special Situations Report Form and faxed/emailed to [redacted] (contact information listed below) within 24 hours of knowledge of the event. All AEs associated with the Special Situations Report Form should be reported as AEs or SAEs as well as recorded on the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

Safety Contact Information:

[redacted]

8.4 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5 Genetics and/or Pharmacogenomics

Genetics are not evaluated in this study.

8.6 Biomarkers

Collection of biological samples for biomarker research is also part of this study. Urine samples for biomarker research are required and will be collected from all patients in this study as specified in the SoA (Section 1.3).

8.7 Immunogenicity Assessments

Immunogenicity assessments are not evaluated in this study.

8.8 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

No formal hypothesis testing is planned for this study.

9.2 Sample Size Determination

Note: "Enrolled" patients are those who have been randomized to a treatment arm.

No formal sample size determination was made for this study, whose primary endpoint is safety and tolerability. Approximately 60 patients will be randomized at approximately 38 clinical sites. Patients (n=20 in each arm) will be randomized to receive PSL [redacted] or placebo.

Sample size estimates are based on a one-sided test at the 0.05 level to detect suppression of viral load to undetectable levels based on the viral load data from the CHARMS study of multivirus-specific T cells for patients with a plasma BK viral load <2000 copies/mL.

Patients will be stratified by screening BK viral load at randomization to ensure equal randomization among active and placebo arms for patient populations [redacted] A minimum of 6 patients must be enrolled in each stratum, but the remaining patients can be enrolled in either stratum.

9.3 Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Population	Description
Intent-to-Treat (ITT)	All randomized patients regardless of whether the patient receives PSL or placebo. Patients will be analyzed according to the randomized study treatment.
Safety	All randomized patients who receive PSL or placebo. All safety analyses will be based on the Safety Population. Patients will be analyzed according to the treatment actually received.

9.4 Statistical Analyses

The SAP will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

Summary statistics will be presented by treatment group. Unless otherwise stated, continuous variables will be summarized using the number of non-missing observations, arithmetic mean, standard deviation, median, minimum, and maximum values as descriptive statistics. Categorical variables will be summarized using the frequency count and the percentage of patients in each category as descriptive statistics.

9.4.2 Primary Endpoint(s)

The primary endpoint is safety and tolerability, as assessed by a qualitative analysis of -treatment emergent adverse events (TEAEs) and changes in vital signs, physical examinations, clinical laboratory assessments, and ECGs.

9.4.3 Secondary Endpoints

The key secondary endpoint is change in BK viremia in patients receiving PSL compared to patients receiving placebo, based on quantitation of viremia performed at the central laboratory.

9.4.4 Tertiary/Exploratory Endpoint(s)

Exploratory continuous and categorical efficacy endpoints will be summarized descriptively by treatment group and dose cohort using the Intent-to-Treat (ITT) Population. Categorical endpoints will be summarized using number and percentage of patients within each category. For time-to-event variables, the Kaplan-Meier method will be used to estimate the median time (days) and its 95% confidence interval.

9.4.5 Safety Analysis

All safety data will be summarized by treatment arm actually received. Categorical endpoints will be summarized using number and percentage of patients within each category. Continuous endpoints will be summarized descriptively with summary statistics (number, mean, standard deviation, standard error, median, first quartile, third quartile, minimum, and maximum).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. A TEAE is defined as an AE with a start date and time on or after the first dose of study treatment and through the Week 24 visit. Treatment-emergent AEs will be summarized by System Organ Class and Preferred Term and further by severity (according to the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v5.0) and relationship to study treatment. The incidence of SAEs will be summarized.

The incidence of AESIs including acute GVHD, CRS, infusion reactions and their corresponding exact binomial confidence intervals with 95% confidence level will be presented by treatment group. Grading criteria for GVHD and CRS are in Appendix 5 in Section 10.5 and Appendix 6 in Section 10.6, respectively.

Descriptive statistics will be provided for relevant laboratory, vital sign, and ECG data. Abnormal laboratory results will be graded according to NCI CTCAE v5.0, if applicable. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-baseline value according to the NCI CTCAE grade, will be provided for selected clinical laboratory tests.

Clinical safety laboratory parameters will be presented in summary tables. Changes from baseline in laboratory parameters, vital sign parameters, and quantitative ECG parameters will be summarized. Selected laboratory parameters will be summarized in shift tables.

Statistical comparisons will be carried out using Fisher's exact test and Student's t test. A 1-sided $P<.05$ will be considered statistically significant. Key secondary outcomes such as BK viral load assessments and change in eGFR (measured by comparing the slope of decline in the eGFR over time) between the placebo group and treatment group will be analyzed using the statistical comparisons described above. The baseline demographics of patients, such as age and gender, etc., will also be analyzed to ensure adequate randomization.

9.4.6 Other Analyses

In addition to the endpoints described previously, the following endpoints may be analyzed:

- Frequency and severity (adjudicated Banff classification) of biopsy-proven acute allograft rejection in recipients of PSL versus placebo.
- Number of patients in the investigational arms with polyomavirus haufen in the urine as compared to the placebo arm.
- Quantification of IFN-ɣ (+) T cells specific for BK virus in patients in the investigational arms as compared to the placebo arm.
- Levels of (virus-specific T cell) donor T cell deoxyribonucleic acid (DNA) as compared to patient T cell DNA in peripheral blood.
- Time to resolution of non-BK target viral infections (ie, associated signs, symptoms, and presence/absence of HHV-6, EBV, JCV, and/or AdV viremia) present at the time of randomization.
- Use of immunosuppressive agents, including specific immunosuppressive agents used, dosed, and any changes in dose.
- Number of hospitalizations/re-hospitalizations for any reason and number of days.
- Incidence and duration of use of any other antiviral therapies during the study.
- Time to death (from any cause) from the time of randomization.
- Number of patients with kidney injury requiring hemodialysis.
- Rate of decline of BK viremia in recipients of PSL using different dosing intervals versus that in patients receiving placebo.
- Assessment of renal function (eGFR estimated by the creatinine-cystatin C method).

Details of these analyses are provided in the SAP.

9.5 Interim Analyses

Administrative interim analyses are planned for the study. The Sponsor's study team and Investigators will remain blinded to individual patient data during and after the administrative interim analyses. All administrative interim analyses will be conducted by the Sponsor.

- The first administrative interim analysis will be performed by the Sponsor when 12 patients in Stratum 1 [redacted] have completed 8 weeks in the study.
- The second administrative interim analysis will be performed when 30 patients have completed 8 weeks in the study.
- Interim analyses may be omitted or added at the discretion of the Sponsor to allow for long term planning, and to assess ending the study or either arm early.

9.5.1 Stopping Criteria

9.5.1.1 Stopping Criteria for Individual Patients

As GVHD and CRS are theoretical safety concerns associated with administration of third-party allogeneic T cells, the incidence and severity of GVHD and CRS will be monitored during the study.

No patients will be permitted to receive a second infusion of PSL or placebo if they develop new onset GVHD ≥Stage 1 or CRS Grade >2 at the proposed time of infusion of any subsequent dose.

After the first 3 doses, patients who have undetectable BK plasma viral load at 2 or more consecutive assessments at least 2 weeks apart will discontinue PSL infusions.

9.5.1.2 Stopping Criteria for the Study

Randomization into the study will be halted if 3 patients experience SAEs that meet the following criteria:

- ≥CTCAE Grade 3,
- Considered related by the Investigator,
- Occur during Period 1 following the initial dose, AND
- Cannot be reasonably attributed to the patient's underlying disease, other medical condition, or concomitant medications.

If this occurs, randomization will not resume until the DSMB has thoroughly reviewed all safety data to date and concluded that it is safe for the study to continue.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study patients.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the patient and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the patient.

10.1.4 Data Protection

- Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Committee Structure

10.1.5.1 Data Safety and Monitoring Board

An independent DSMB will be convened for this study to routinely monitor patient safety and evaluate prespecified interim analyses to stop the study or either arm early. The DSMB will receive summary reports of all unexpected SAEs. A DSMB charter, detailing all aspects of the DSMB's composition, scope of review, and procedures will be provided in a separate document. In addition, the DSMB will review safety data after the first 3 patients enrolled have received their 3rd dose.

An unblinded statistician will be assigned to the DSMB. This statistician will not be involved in any aspects of study conduct outside of the DSMB, and their role will be defined in the DSMB charter.

10.1.6 Dissemination of Clinical Study Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB/IEC as appropriate. Patients or their

legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

10.1.7 Data Quality Assurance

- All patient data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the case report form (CRF).
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 5 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the

study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of patients.

The first act of recruitment is the first patient randomized, and will be the study start date.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study treatment development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of patients by the Investigator
- Total number of patients included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

10.1.10 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal and/or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 4 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 4 Protocol-Required Safety Laboratory Tests

Laboratory Tests	Parameters			
Hematology	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	White blood cell (WBC) count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry	Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT)	Total Protein
	Glucose, nonfasting	Calcium	Alkaline phosphatase	Cystatin C
	Chloride	Gamma-glutamyl transferase	Lactate dehydrogenase	Uric acid
	Albumin	Amylase	Bicarbonate	Creatine kinase
	Inorganic phosphorus	Lipase		
Plasma Viral load	Adenovirus	BK virus	Cytomegalovirus	Epstein-Barr virus (in PBMCs)
	Human herpesvirus 6	JC virus		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	• Highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)			
Other Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serology (human immunodeficiency virus [HIV] antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) along with confirmatory tests if requested • All study-required laboratory tests will be performed by a central laboratory, with the exception of the following tests that will be shipped to the central lab and then sent to specialty labs: o Urinary haufen o Donor specific antibodies o Testing of banked peripheral blood mononuclear cells (PBMCs) for virus specific immunity o Testing of banked PBMCs for donor DNA			

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study patient, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

• **Definition of Unsolicited and Solicited AE**
• An unsolicited AE is an AE that was not solicited using a Patient Diary and that is communicated by a patient who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. • Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The patient will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of patient concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the patient's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by patient will be collected during interview with the patient and by review of available medical records at the next visit. • Solicited AEs are predefined local and systemic events for which the patient is specifically questioned, and which are noted by the patient in their diary.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any serious AE that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the patient has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the patient's medical records to [redacted] in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by [redacted]. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to [redacted].
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Assessment of Intensity

The severity of all AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. For those AE terms not listed in the CTCAE, the following grading system should be used:

- CTCAE Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- CTCAE Grade 2: Moderate; minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- CTCAE Grade 4: Life-threatening consequences; urgent intervention indicated
- CTCAE Grade 5: Death related to the AE

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to [redacted]. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to [redacted]
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by [redacted] to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide [redacted] with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to [redacted] within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to ICON PVSS via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to [redacted] will be the electronic data collection tool.

- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor by telephone.
- Contacts for SAE reporting can be found in Section 8.3.7.1.

Initial Reports

- All SAEs occurring from randomization until study participation is complete or until resolution must be reported to [redacted] within 24 hours of awareness. After study participation is complete, any SAE that the Investigator considers related to study treatment must be reported to [redacted] or the Sponsor/designee.
- To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, [redacted] Safety personnel will be notified electronically by the EDC system and will retrieve the form.

Follow-Up Reports

- The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.
- Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any redacted supporting documentation (eg, patient discharge summary or autopsy reports) to [redacted] via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined below.

SAE Reporting to ICON PVSS via Paper Data Collection Tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the [redacted].
- If the event meets serious criteria and it is not possible to access the EDC system, send an email to [redacted] at [redacted] email address [redacted] or call the [redacted] SAE reporting line (phone number [redacted], and fax/email the completed paper SAE form to [redacted] (contact information listed in Section 8.3.7.1)

within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in Section 8.3.7.1.

10.4 Appendix 4: Contraceptive and Barrier Guidance

10.4.1 Definitions

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
        - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
    - Permanent sterilization methods (for the purpose of this study) include:
        - Documented hysterectomy
        - Documented bilateral salpingectomy
        - Documented bilateral oophorectomy
        - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

    Note: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

    - If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study treatment, additional evaluation should be considered.

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

3. Premenopausal female with permanent infertility due to one of the following:
    a. Documented hysterectomy
    b. Documented bilateral salpingectomy
    c. Documented bilateral oophorectomy

d. For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

4. Postmenopausal female
   a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
      i. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement >40 IU/L or mIU/mL is required.
      ii. Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2 Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation [c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS) [c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male patient can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.*)*
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral – intravaginal – transdermal – injectable
Progestogen-only hormone contraception associated with inhibition of ovulation [c] – oral – injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.)*
Effective Methods[d] That Are Not Considered Highly Effective *Failure rate of ≥1% per year when used consistently and correctly.*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[e]
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c.) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. d) Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. e) Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 Appendix 5: Graft Versus Host Disease Scales

Table 5 MAGIC Criteria for Staging and Grading of Acute Graft Versus Host Disease

Stage	Skin (Active Erythema Only)	Liver (Bilirubin)	Upper GI	Lower GI (Stool Output/Day)
0	No active (erythematous) GVHD rash	<2 mg/dL	No or intermittent nausea, vomiting, or anorexia	Adult: <500 mL/day or <3 episodes/day. Child: <10 mL/kg per day or <4 episodes/day.
1	Maculopapular rash <25% BSA	2-3 mg/dL	Persistent nausea, vomiting, or anorexia	Adult: 500-999 mL/day or 3-4 episodes/day. Child: 10-19.9 mL/kg per day or 4-6 episodes/day.
2	Maculopapular rash 25%-50% BSA	3.1-6 mg/dL	-	Adult: 1000-1500 mL/day or 5-7 episodes/day. Child: 20-30 mL/kg per day or 7-10 episodes/day.
3	Maculopapular rash >50% BSA	6.1-15 mg/dL	-	Adult: >1500 mL/day or >7 episodes/day. Child: >30 mL/kg per day or >10 episodes/day.
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation >5% BSA	>15 mg/dL	-	Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume).

Overall clinical grade (based on most severe target organ involvement):
Grade 0: No Stage 1 to 4 of any organ.
Grade I: Stage 1 to 2 skin without liver, upper GI, or lower GI involvement.
Grade II: Stage 3 rash and/or Stage 1 liver and/or Stage 1 upper GI and/or Stage 1 lower GI.
Grade III: Stage 2 to 3 liver and/or Stage 2 to 3 lower GI, with Stage 0 to 3 skin and/or Stage 0 to 1 upper GI.
Grade IV: Stage 4 skin, liver, or lower GI involvement, with Stage 0 to 1 upper GI.

Abbreviations: BSA = body surface area; GI = gastrointestinal; GVHD = graft versus host disease; MAGIC = Mount Sinai Acute GVHD International Consortium

Source: Harris AC, Young R, Devine S, et al. International, multicenter standardization of acute graft-versus-host disease clinical data collection: a report from the Mount Sinai Acute GVHD International Consortium. Biol Blood Marrow Transplant. 2016;22(1):4-10.

Table 6 Response Definitions for Acute Graft Versus Host Disease

Response Term	Definition
CR	Complete resolution of all signs and symptoms of GVHD in all organs without intervening salvage therapies.
PR	Improvement of 1 stage in 1 or more organs involved by GVHD without progression in others.
Mixed response	Improvement in at least 1 involved organ with progression or newly developed GVHD in 1 or more organs.
Progression	Worsening in 1 or more organs by 1 or more stage without improvement in any involved organ.
NR	No improvement or deterioration in any organ within 14 days of therapy initiation.

Abbreviations: CR = complete response; GVHD = graft versus host disease; NR = no response; PR = partial response.
Source: Center for International Blood & Marrow Transplant Research (CIBMTR). Clinical trial endpoints for patients with acute GVHD. 2009. https://www.cibmtr.org/Meetings/Materials/GVHDworkshop/pages/index.aspx.

10.6 Appendix 6: Cytokine Release Syndrome Scale

Table 7 Cytokine Release Syndrome Scale

Grade CRS Parameter	1	2	3	4
Fever [1]	≥38.0°C	≥38.0°C	≥38.0°C	≥38.0°C
With				
Hypotension	None	Not requiring vasopressors	Requiring vasopressors with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or [2]				
Hypoxia	None	Requiring lowflow nasal cannula (oxygen delivered at ≤6 L/minute) or blowby	Requiring highflow nasal cannula (oxygen delivered at >6 L/minute), facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation, mechanical ventilation)

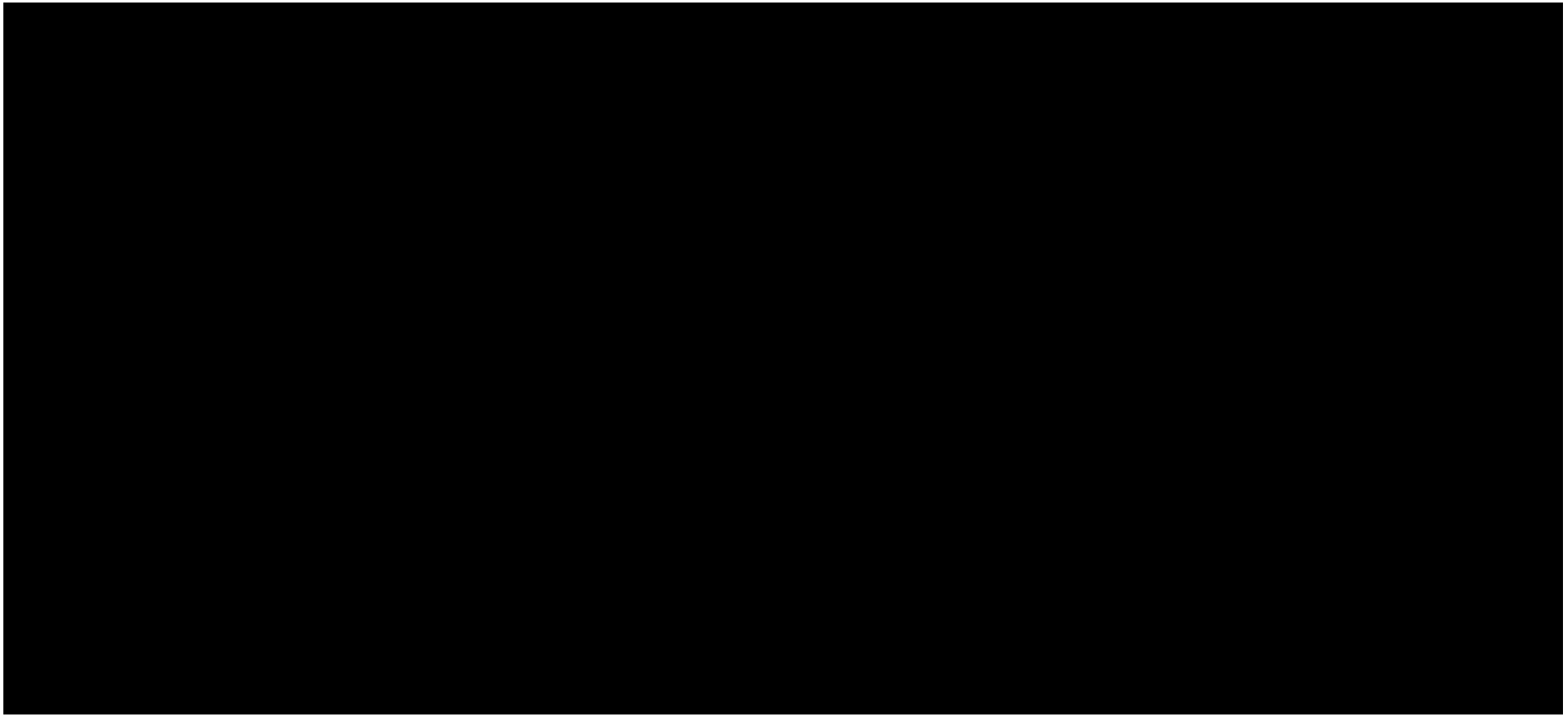
Note: Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.
Note: Grade 5 CRS is defined as death due to CRS, in which another cause is not the principle factor leading to the outcome.

1 Fever is defined as temperature ≥38.0°C not attributable to any other cause. In patients who have CRS and then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

2 CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

Abbreviations: BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events.
Source: Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25(4):625-638.

10.7 Appendix 7: Modification of Immunosuppression



NOTE: *Viral load determinations that would lead to changes in immunosuppression (red boxes) should be repeated immediately upon receipt to confirm that action should be taken as indicated.

a If MMF has already been reduced or discontinued more than 28 days prior, proceed to the next step in the algorithm. Other variations from the algorithm require consultation with, and approval by, the Sponsor's Medical Monitor.
b Triple Immunosuppression: low-dose oral steroids, MMF, and calcineurin inhibitor.
c Double Immunosuppression: MMF and calcineurin inhibitor.

Abbreviations: AST = American Society of Transplantation; KDIGO = Kidney Disease: Improving Global Outcomes; MMF = mycophenolate mofetil; PCR = polymerase chain reaction; PI = Principal Investigator (ie, Investigator); Q =e very; VL = viral load

11 REFERENCES

Bohl DL, Brennan DC. BK virus nephropathy and kidney transplantation. Clin J Am Soc Nephrol. 2007 Jul;2 Suppl1:S36-46.

Bruminhent J, Srisala S, Klinmalai C, Pinsai S, Watcharananan SP, Kantachuvesiri S, et al. BK polyomavirus-specific T cell immune responses in kidney transplant recipients diagnosed with BK polyomavirus-associated nephropathy. BMC Infect Dis. 2019 Nov 19;19(1):974.

Center for International Blood & Marrow Transplant Research (CIBMTR). Workshop on Clinical Trial Endpoints for Acute Graft-vs-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation. Clinical trial endpoints for patients with acute GVHD. 2009. Accessed: 27 May 2020. www.cibmtr.org/Meetings/Materials/GVHDworkshop/GvHD%20Workshop%20Library/08_Alousi_FDAaGVHDwrkshp_May09.pdf

DeWolfe D, Gandhi J, Mackenzie MR, Broge TA, Bord E, Babwah A, et al. Pre-transplant immune factors may be associated with BK polyomavirus reactivation in kidney transplant recipients. PLoS One. 2017 May 31;12(5): e0177339.

El-Husseini A, Hassan W, Yaseen M, Suleiman B, Saleh S, Malik O, et al. Impact of human leukocyte antigen and calculated panel reactive antibody on BK viremia in kidney transplant recipients: a single-center experience and literature review. Transpl Infect Dis. 2019 Aug;21(4):e13071.

Favi E, Puliatti C, Sivaprakasam R, Ferraresso M, Ambrogi F, Delbue S, et al. Incidence, risk factors, and outcome of BK polyomavirus infection after kidney transplantation. World J Clin Cases. 2019 Feb 6;7(3):270-90.

Flower A, Ayello J, Harrison L, Morris E, Sturhahn M, Maryamchik E, et al. The safety and efficacy of targeted virus specific cytotoxic T-lymphocytes (VST) manufactured by the IFN-ɣ cytokine capture system (CCS) for the treatment of refractory adenovirus (ADV), cytomegalovirus (CMV), Epstein Barr virus (EBV) and BK virus (BKV) in children, adolescents and young adults (CAYA) after allogenic hematopoietic stem cell transplantation (Allo-HSCT), solid organ transplantation (SOT), or with primary immunodeficiency (PID). Abstract 96. 2020 Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR. Orlando, Florida. Feb 19-23, 2020. https://tct.confex.com/tct/2020/meetingapp.cgi/Paper/15167

Gardner SD, Mackenzie EFD, Smith C, Porter AA. Prospective study of the human polyomaviruses BK and JC and cytomegalovirus in renal transplant recipients. J Clin Pathol. 1984 May;37(5):578-86.

Goldberg RJ, Weng FL, Kandula P. Acute and chronic allograft dysfunction in kidney transplant recipients. Medical Clinic North Am. 2016 May;100(3):487-503.

Harris AC, Young R, Devine S, Hogan WJ, Ayuk F, Bunworasate U, et al. International, multicenter standardization of acute graft-versus-host disease clinical data collection: a report from the Mount Sinai Acute GVHD International Consortium. Biol Blood Marrow Transplant. 2016 Jan;22(1):4-10.

Hirsch HH, Randhawa P, and the AST Infectious Diseases Community of Practice. BK polyomavirus in solid organ transplantation. Am J Transpl. 2013 Mar;13 Suppl 4:179-88.

Jawdeh BGA, Govil A. Acute kidney injury in transplant setting: differential diagnosis and impact on health and health care. Adv Chronic Kidney Dis. 2017 Jul;24(4):228-32.

Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019 Apr;25(4):625-38.

Mueller K, Schachtner T, Sattler A, Meier S, Friedrich P, Trydzenskaya H, et al. BK-VP3 as a new target of cellular immunity in BK virus infection. Transplantation. 2011 Jan 15;91(1):100-7.

Muftuoglu M, Olson A, Marin D, Ahmed S, Mulanovich V, Tunmala S, et al. Allogenic BK virus-specific T cells for progressive multifocal leukoencephalopathy. N Engl J Med. 2018 Oct 11; 379(15):1443-51.

Prockop S, Hiremath M, Ye W, Gamelin L, Navarro W, Mahadeo M. A multicenter, open-label, phase 3 study of tabelecleucel for solid organ transplant subjects with Epstein-Barr virus-driven post-transplant lymphoproliferative disease (EBV PTLD) after failure of rituximab or rituximab and chemotherapy. Blood. 2019;134(Suppl 1):5326.

Sawinski D, Forde KA, Trofe-Clark J, Patel P, Olivera B, et al. Persistent BK viremia does not increase intermediate-term graft loss but is associated with de novo donor-specific antibodies. J Am Soc Nephrol. 2015 Apr;26(4):966-75.

Schachtner T, Babel N, Reinke P. Different risk factor profiles distinguish early-onset from late-onset BKV-replication. Transpl Int. 2015 Sep;28(9):1081-91.

Schmidt T, Adam C, Hirsch HH, Janssen MWW, Wolf M, Dirks J, et al. BK polyomavirusspecific cellular immune responses are age-dependent and strongly correlate with phases of virus replication. Am J Transplant. 2014;14:1334-5.

Tzannou I, Watanabe A, Niak S, Daum R, Kuvalekar M, Leung KS, et al. “Mini” bank of only 8 donors supplies CMV-directed T cells to diverse recipients. Blood Adv. 2019 Sep 10;3(17):2571-80.

Tzannou I, Papadopoulou A, Naik S, Leung K, Martinez CA, Ramos CA, et al. Off-the-shelf virus-specific T cells to treat BK virus, human herpesvirus 6, cytomegalovirus, Epstein-Barr virus, and adenovirus infections after allogeneic hematopoietic stem-cell transplantation. J Clin Oncol. 2017 Nov 1;35(31):3547-57.

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